Nephrol Dial Transplant (2002) 17: 1558–1563

Nephrology
Dialysis
Transplantation

Invited Comment

Uraemic pruritus—new perspectives and insights from recent trials

Thomas Mettang[1], Christiane Pauli-Magnus[2] and Dominik Mark Alscher[1]

[1]Robert-Bosch-Hospital Stuttgart, Department of Internal Medicine, Division of General Internal Medicine and Nephrology, Stuttgart, Germany and [2]University Hospital, Division of Clinical Pharmacology, Department of Medicine, Zürich, Switzerland

Keywords: end-stage renal disease; therapy; trials; uraemic pruritus

Introduction

Uraemic pruritus (UP) remains a frequent and sometimes tormenting problem in patients with advanced or end-stage renal disease [1]. Many attempts have been made to relieve this bothersome symptom in affected patients, however with generally limited success. Whenever a new treatment option is reported to be effective, some time elapses before conflicting results are published; in the meantime, the mood of patients and physicians changes from euphoria to disillusionment. This happened with erythropoetin [2,3] and naltrexone [4,5], the last propagated treatment modalities in this respect.

The main obstacle in the effort to create effective treatment modalities is the incomplete knowledge of the underlying pathophysiological mechanisms. Furthermore, given the great clinical heterogenicity of UP, systematically performed studies are hard to obtain and are therefore sparse.

Clinical features of uraemic pruritus

The intensity and spatial distribution of pruritus varies significantly over time and some patients are affected to a varying degree throughout the duration of their renal disease. The intensity of UP ranges from sporadic discomfort to complete restlessness during both the day- and night-time. Initially, patients with UP do not show any changes in skin appearance. Excoriation by scratching with or without impetigo can occur as a secondary phenomenon and rarely prurigo nodularis or Kyrle's disease is observed (Figure 1a–d). There are interindividual differences in spatial distribution of UP: 25–50% of patients with UP complain about generalized pruritus [6,7]. In the remaining patients, UP seems to predominantly affect the back, the face and the shunt arm, respectively [8]. In ~25% of patients with UP, pruritus is most severe during or immediately after dialysis [8].

Incidence of uraemic pruritus

Whereas in the beginnings of dialysis treatment UP was a very common problem, it appears that its incidence has declined over the past 20 years. In the early 1970s, Young and co-workers reported that ~85% [9] of patients were affected by UP. This number decreased to 50–60% in the late 1980s [10]. A recent investigation in Germany showed that only 22% of all dialysis patients complained about pruritus at the time they were questioned [5]. Some of the representative studies are shown in Table 1.

Interestingly, severe pruritus is very rare in paediatric patients on dialysis. This could be shown by a systematic review of almost all German paediatric dialysis centres involving 199 children, where only 9.1% of the children on dialysis complained about pruritus. Moreover the intensity was not very severe in the affected patients [11] (Figure 2).

Pathophysiological concepts of uraemic pruritus

In the past 20 years different hypotheses on the pathophysiology of UP have been generated. The most prominent concept focused on parathyroid hormone (PTH) as a culprit compound, because UP seemed to be most severe in patients with marked hyperparathyroidism and resolved after parathyroidectomy [12,13]. However, subsequent data could not confirm this theory [14]. Similarly, the concept of precipitated calcium phosphate crystals in the setting of elevated serum calcium and phosphate levels as a responsible event in UP could not be sustained [15]. Recently controversy arose as to whether the histamine secreted by proliferated mast cells might cause UP [16]. However, like the concepts mentioned above, the

Correspondence and offprint requests to: Thomas Mettang, Robert-Bosch-Krankenhaus, Auerbachstrasse 110, D-70376 Stuttgart, Germany. Email: Thomas.Mettang@rbk.de

Fig. 1. (**a**–**d**) Skin affected in patients with uraemic pruritus. (**a**) Scratches on the arm hosting the fistula. (**b**) Deep scars on the shoulders and the back of a female patient on haemodialysis. (**c**) Prurigo nodularis with excoreations and superinfection on the forearm of a patient on peritoneal dialysis. (**d**) Kyrles disease on the back of a patient on haemodialysis.

'histamine story' ceased because of conflicting results [10,17,18].

At present, two new concepts with respect to UP are being discussed and are presented in detail below.

The 'immuno-hypothesis'

Due to several observations and information from other studies, there is increasing evidence that UP is a systemic rather than an isolated skin disease, and that derangements of the immune system with a pro-inflammatory pattern may be involved in the pathogenesis of UP. This hypothesis is supported by several lines of evidence.

Gilchrest *et al.* [19] showed that tanning patients with ultra violet (UV) B light led to relief of UP in a considerable number of patients. This effect could be demonstrated even when only half of the body was irradiated. This observation led to the assumption that UVB radiation has a systemic effect. Interestingly,

Table 1. Prevalence of uraemic pruritus reported in the literature

Study	Prevalence % (*n*)		Anamnestic % (*n*)		Statistical relevance
	HD	CAPD	HD	CAPD	
Young (1973)	86 (86)				
Altmeyer (1982)	78 (28)				
Gilchrest (1982)	37 (237)			41 (237)	
Bencini (1985)	41 (54)	16 (19)			HD > CAPD
Matsumoto (1985)	57 (51)				
Parfrey (1988)	49	50 (97)			NS
Bäckdahl (1988)	66 (29)				
Mettang (1990)	64 (28)	50 (26)	17 (28)	21 (26)	NS
Albert (1991)	54 (71)	48 (79)			NS
Balaskas (1993)	54 (76)	62			NS
Pauli-Magnus (1999)	22 (378)	43 (44)			CAPD > HD

HD = haemodialysis; CAPD = continuous ambulatory peritoneal dialysis; NS = not significant.

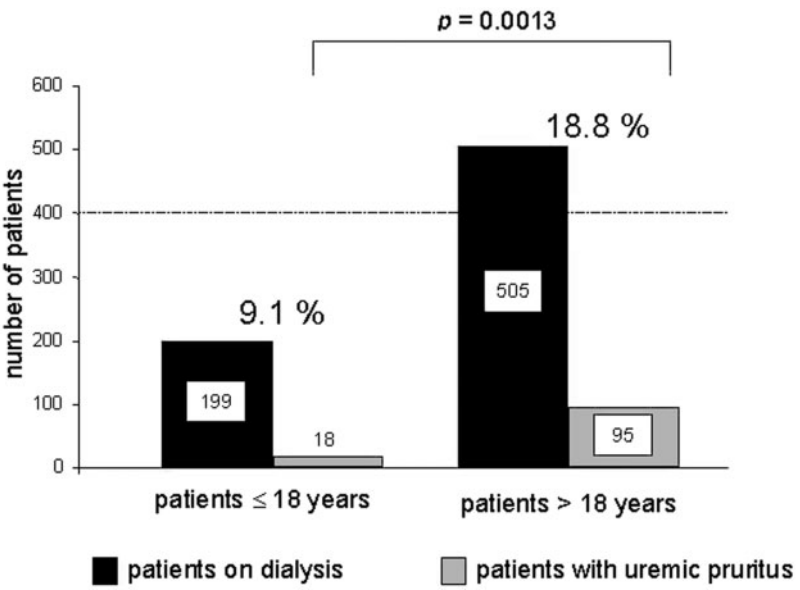

Fig. 2. Prevalence of uraemic pruritus in children on dialysis (18 years or younger) and in adult dialysis patients (older than 18 years). The prevalence of uraemic pruritus in children is significantly lower than in adult patients (χ^2 test; Schwab *et al.*, unpublished data).

UVB exposure was shown to be a pronounced modulator of Th1 and Th2 lymphocyte differentiation and to attenuate Th1 expression [20].

Some studies have shown that increasing the dose of dialysis leads to an improvement in UP [21]. Consequently, the lower incidence of UP over recent decades has been attributed to the improvement of dialysis modalities. Increasing concerns about the adequate dialysis dose and the wide use of Kt/V- or creatinine clearance-guided dialysis regimens might have contributed to the decreased incidence of UP. Additionally, dialysis efficacy has increased following the use of high flux dialysis membranes with larger surfaces and improved biocompatibility with the introduction of synthetic fibres, such as polysulfone or polyacrylnitrile. These new materials activate complement and leukocytes to a much lesser degree than conventional, less biocompatible materials such as cuprophane, with less generation of proinflammatory cytokines [22].

It has been shown that thalidomide and tacrolimus (as an ointment) are effective in the therapy of UP, at least to a certain degree [23,24]. Thalidomide, which is currently used as an immunomodulator to treat graft-versus-host reactions, suppresses TNF-α production and leads to a predominant differentiation of Th2 lymphocytes with suppression of interleukin-2 (IL-2)-producing Th1 cells [25]. A similar effect can be observed with tacrolimus, which also suppresses differentiation of Th1-lymphocytes and ensuing IL-2 production [26].

After kidney transplantation patients almost never complain about UP as long as immunosuppressive therapy including cyclosporin is administered, even when a substantial loss of transplant function has occurred [27].

The bottom line of all these observations is that they point to a substantial role of immunological mechanisms in the pathogenesis of UP. Numerous factors are probably involved, the most likely culprit being IL-2, which is secreted by activated Th1 lymphocytes. In coping with this hypothesis, patients receiving IL-2 for the treatment of malignant disease frequently report tormenting pruritus [28]. Additionally it has been shown that intradermally applied IL-2 had a rapid, although weak pruritogenic effect [29].

To investigate further the hypothesis that IL-2 is causally linked to UP cytokine and T cell differentiation, patterns should be determined in patients with and without UP. Additionally, T-cell differentiation and cytokine pattern should be investigated in children on dialysis who rarely complain about UP. It has been reported that older individuals are more likely to differentiate T helper cells towards Th1 than younger individuals [30].

Preliminary results of a multicentre study initiated by our group revealed that patients with UP exhibited a more pronounced Th1 differentiation than patients without UP, as determined by measuring intracytoplasmatic TNF-α in CD4 cells. These results may support the hypothesis that an inflammatory state may convey UP.

The 'opioid hypothesis'

This pathogenetical concept that changes in the opiodergic system might be involved in the pathophysiology of pruritus concept was first developed for cholestatic pruritus and supported by different lines of evidence: First, several μ-receptor-agonistic drugs are known to induce pruritus, particularly after central administration [31,32]. Secondly, it could be demonstrated in animal studies that cholestasis is associated with an increased opioidergic tone [33,34]. Thirdly, administration of opiate antagonists was successful in the treatment of cholestatic pruritus [35,36]. It was suggested that cholestatic pruritus may be mediated by pathological changes in the central nervous system. This hypothesis was supported by the findings that a global down-regulation of μ-receptors occurred in the brain of cholestatic rats [37] and that in patients with chronic cholestasis, an opiate withdrawal-like syndrome was precipitated by administration of an oral opiate-antagonist [38].

In 1985 there was a first case report describing successful treatment of uraemic pruritus by intravenous administration of the opiate-antagonist naloxone [39]. The therapeutic use of opiate antagonists in patients with UP was based on the assumption that endogenous opiate peptides may also be involved in the pathogenesis of UP. A subsequent placebo-controlled clinical trial by Peer *et al.* [4] showed that administration of the oral μ-receptor-antagonist naltrexone was associated with a significant decrease in pruritus perception in all of the treated patients with severe uraemic pruritus. However, the number of patients studied was small and the treatment period (1 week) was short.

When trying to confirm the data from Peer *et al.* [5] in a larger cohort (23 patients with moderate to severe UP) treated for a longer time period (4 weeks), we failed to obtain any statistically significant response to naltrexone.

Recently, Kumagai developed the hypothesis that the activation of κ-receptors expressed by dermal cells and lymphocytes may lead to the suppression of pruritus sensation. Therefore, when these receptors are not adequately stimulated or μ-receptors are overexpressed, patients may experience more severe itching. Consequently the authors are about to test whether κ-receptor-agonists (TRK-820) are able to reduce UP; their preliminary results appear to be encouraging (Hiroo Kumagai, personal communication).

Considering the conflicting results mentioned above, it remains to be established whether the opioidergic system plays a significant role in the pathophysiology of uraemic pruritus.

Therapeutic options

As stated above, therapeutic options for UP are sparse. Most of the success stories turned into reports of failure. Based on the above-mentioned pathophysiological concepts, we will focus on two recent modalities that were studied extensively by our group: (i) local treatment with tacrolimus ointment; and (ii) systemic treatment with naltrexone, a μ-receptor antagonist.

Local treatment with tacrolimus ointment

Due to our inability to help some severely tormented UP patients, we decided to take a new approach. It has been shown previously that administering tacrolimus ointment to the skin of patients with atopic dermatitis leads to complete or partial resolution of illness-related symptoms [40]. Three patients on peritoneal dialysis with severe UP who had frustratingly been pre-treated with other potentially effective modalities were recruited. The patients documented pruritus using a visual analogue scale (VAS), ranging from 0 to 10, and a detailed pruritus score 3 days prior to and during the treatment phase. Patients were instructed to apply a 0.03% tacrolimus ointment twice daily to the areas most affected by UP for a period of 7 days.

In all three patients, UP could be reduced dramatically from the very start of treatment (Figure 3). Two days after discontinuation of treatment, pruritus slowly recurred. No side-effects were observed during or after the treatment period [24].

Tacrolimus ointment seems to be a safe and highly effective short-term treatment option for patients suffering from severe UP. However, considering the potentially carcinogenic effect of systemically administered tacrolimus, one should be cautious in treating patients over longer periods of time.

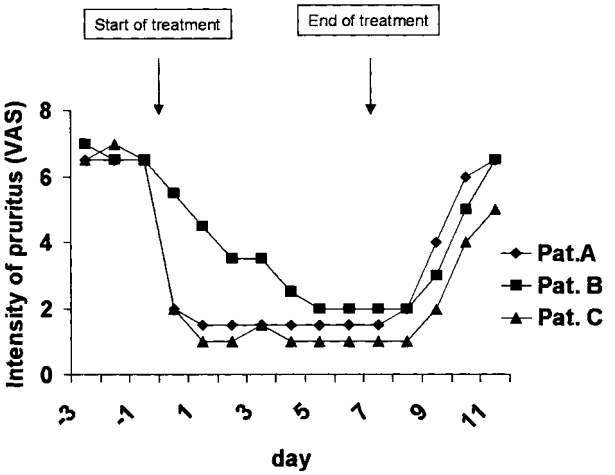

Fig. 3. Treatment of uraemic pruritus with tacrolimus ointment in three patients with otherwise refractory pruritus [24].

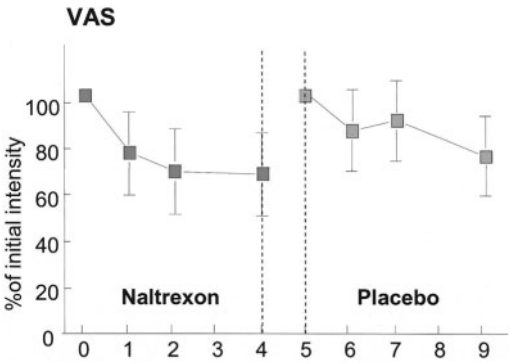

Fig. 4. Response of uraemic pruritus in 23 patients during treatment with either 50 mg naltrexone or placebo for 4 weeks. There was no statistically significant difference between the two treatment phases [5].

Systemic treatment with naltrexone, a μ-receptor antagonist

We undertook a placebo-controlled, double-blind crossover study in patients on haemodialysis or peritoneal dialysis with persistent, treatment-resistant pruritus. Of 422 patients screened between December 1997 and June 1998, 93 suffered from pruritus and 23 were eligible for the study. Patients started either with a 4-week naltrexone sequence (50 mg/day) or matched placebo. There was a 7-day washout between the two periods. Pruritus intensity was scored daily using a VAS, and also weekly using a detailed score assessing scratching activity, distribution of pruritus, and frequency of pruritus-related sleep disturbance.

Sixteen of 23 patients completed the study. During naltrexone therapy, pruritus decreased by 29.2% on the VAS and by 17.6% on the detailed score. In comparison, pruritus decreased by 16.9% on the VAS and by 22.3% during placebo period. The difference between the naltrexone- and the placebo-treatment period was not statistically significant (Figure 4). Nine of 23 patients complained about gastrointestinal adverse events during the naltrexone period, in comparison with only one of 23 patients during the placebo period ($P < 0.005$).

The results of Peer *et al.* [4] are in sharp contrast to the results of our study and cannot be explained by differences in patient compliance, naltrexone dose or study design, as both studies were randomized, placebo-controlled, double-blind crossover trials. As in the study by Peer *et al.* [4], subjects included in our trial had long-lasting, treatment-resistant pruritus and no evidence of coexisting dermatologic disease. To exclude factors possibly aggravating uraemic pruritus, such as inadequate dialysis and anaemia, only patients who were considered to be well dialysed and with a haemoglobin level >10 g/dl were included in our trial. We also included patients with evidence of hyperparathyroidism and hyperphosphataemia, as the pathogenetic role of these factors in UP is controversial [41]. However, to exclude a relevant influence of these factors on the effect of naltrexone treatment we performed a subgroup analysis, examining data separately for those with hyperparathyroidism and/or hyperphosphataemia, and those without. Naltrexone treatment was ineffective in all subgroups.

The pathogenesis of UP may be influenced by differences in the management of dialysis patients, and regional differences in life and eating habits in distinct world regions. In the study by Peer *et al.* [4], no details were given on dialysis modalities. Possibly, the involvement of such additional pathogenetic factors led to a higher incidence of severe pruritus and to differences in naltrexone response.

In conclusion, UP remains a clinically important problem in patients on dialysis. The pathogenesis of this bothersome and sometimes tormenting symptom is still obscure. There are hints that derangements of either the opioidergic and/or the immune system are involved. A unifying concept would probably suggest that inflammatory stimuli, conveyed by uraemia and/or dialysis, would lead to both an augmented differentiation of Th1 lymphocytes and subsequently a suppression of itch-reducing κ-receptors or an increase of μ-receptors in the skin of dialysis patients. However, this hypothesis remains unproven at present, and safe and effective therapeutic modalities are lacking. Immunomodulatory and κ-receptor agonistic drugs may well prove helpful in the most severe cases.

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